EXHIBIT 23

SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1 (b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY (Last) (First) (Middle) 3290 WEST BAYSHORE ROAD (Street) PALO ALTO CA 94303 (City) (State) (Zip)	CONNETICS CORP [CNCT] 3. Date of Earliest Transaction (Month/Day/Year) 04/25/2005 4. If Amendment, Date of Original Filed (Month/Day/Year)	Director ☐ 10% Owner X Officer (give title below) ☐ Other (specify below) COO 6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person ☐ Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	04/25/2005		M		2,279	A	$4.5625	26,124	D	
Common Stock, Par Value $0.001	04/25/2005		S		2,279 (1)	D	$28	23,845	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. N of deri Sec Ben Ow Foll Rep Tra (s) (
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Non-Qualified Stock Option (right to buy)	$4.5625	04/25/2005		M			2,279 (2)	01/02/2005	01/02/2011	Common Stock, Par Value $0.001	2,279	$28	6

Explanation of Responses:

1. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

2. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

Remarks:

Charles Gregory Vontz 04/26/2005

** Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director: — 10% Owner: — Officer (give title below): X Other (specify below): — COO
(Last) (First) (Middle): 3290 WEST BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 11/08/2004	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction (s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	11/08/2004		M		4,075	A	$4.5625	27,209	D	
Common Stock, Par Value $0.001	11/08/2004		M		5,925	A	$4.563	33,134	D	
Common Stock, Par Value $0.001	11/08/2004		S		10,000 (1)	D	$27.2055	23,134	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. N of deri Sec Ben Owi Foll Rep Tra (s) (
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Non-Qualified Stock Option	$4.5625	11/08/2004		M			4,075 (2)	11/02/2004	01/02/2011	Common Stock, Par Value	4,075	$27.2055	5

(right to buy)									$0.001				
Non-Qualified Stock Option (right to buy)	$4.563	11/08/2004		M		5,925 (2)	10/12/2004	10/12/2010	Common Stock, Par Value $0.001	5,925	$27.2055	5-	

Explanation of Responses:

1. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

2. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

Remarks:

Charles Gregory Vontz 11/09/2004

** Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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Washington, D.C. 20549

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STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director: 10% Owner; X Officer (give title below): COO; Other (specify below)
(Last) (First) (Middle): 3290 WEST BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 08/09/2004	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction (s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	08/09/2004		M		10,000	A	$4.5625	33,134	D	
Common Stock, Par Value $0.001	08/09/2004		S		10,000 (1)	D	$25.0455	23,134	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. of de Se Be Ow Fo Re Tr (s
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Non-Qualified Stock Option (right to buy)	$4.5625	08/09/2004		M			10,000 (2)	08/02/2004	01/02/2011	Common Stock, Par Value $0.001	10,000	$4.5625	

Explanation of Responses:

1. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

2. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

Remarks:

Charles Gregory Vontz 08/10/2004

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director: — 10% Owner: — Officer (give title below): X (COO) — Other (specify below): —
(Last) (First) (Middle): 3290 WEST BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 05/10/2004	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year): 05/11/2004	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	05/10/2004		M		10,000	A	$4.5625	31,782	D	
Common Stock, Par Value $0.001	05/10/2004		S		10,000 (1)	D	$18.3625	21,782	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. of de S B O F R T (s
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Non-Qualified Stock Option (right to buy)	$4.5625	05/10/2004		M		10,000 (2)		01/02/2002	01/02/2011	Common Stock, Par Value $0.001	10,000	$18.3625	

Explanation of Responses:

1. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

2. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

Remarks:

Charles Gregory Vontz 05/19/2004

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director: — 10% Owner: — Officer (give title below): X Other (specify below): — COO
(Last) (First) (Middle): 3290 WEST BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 05/10/2004	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
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1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	05/10/2004		M		15,000	A	$4.5625	36,782	D	
Common Stock, Par Value $0.001	05/10/2004		S		15,000 (1)	D	$18.3625	21,782	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. of d S B O F R T (s
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Non-Qualified Stock Option (right to buy)	$4.5625	05/10/2004		M			15,000 (2)	01/02/2002	01/02/2011	Common Stock, Par Value $0.001	15,000	$18.3625	

Explanation of Responses:

1. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

2. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

Remarks:

Charles Gregory Vontz 05/11/2004

** Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director: 10% Owner; X Officer (give title below): Chief Operating Officer; Other (specify below)
(Last) (First) (Middle): 3290 W. BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 01/05/2004	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year): 01/05/2004	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
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Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares	
Common Stock, Par Value $0.001	$18.05	01/05/2004		A		112,000 (1)		01/05/2005	01/05/2014	Common Stock, Par Value $0.001	112,000	$18.05

Explanation of Responses:

1. The options were granted under the Connetics Corporation 2000 Stock Plan and are exercisable at the rate of 1/4 on the one year anniversary and 1/48 per month thereafter.

Remarks:

Katrina J. Church attorney in fact for Charles Gregory Vontz — 01/12/2004

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director: 10% Owner; X Officer (give title below): Chief Operating Officer; Other (specify below)
(Last) (First) (Middle): 3290 W. BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 01/02/2004	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

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			Code	V	Amount	(A) or (D)	Price			

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares	
Common Stock, Par Value $0.001	$18.05	01/02/2004		A		112,000 (1)		01/02/2005	01/02/2014	Common Stock, Par Value $0.001	112,000	$18.05

Explanation of Responses:

1. The options were granted under the Connetics Corporation 2000 Stock Plan and are exercisable at the rate of 1/4 on the one year anniversary and 1/48 per month thereafter.

Remarks:

Charles Gregory Vontz 01/05/2004

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

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SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1 (b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director; 10% Owner; X Officer (give title below); Other (specify below); Chief Operating Officer
(Last) (First) (Middle): 3290 W. BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 12/10/2003	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	12/10/2003		M		15,000	A	$4.563	36,782	D	
Common Stock, Par Value $0.001	12/10/2003		S		15,000 (1)	D	$16.5645	21,782	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. of de Se Be Ow Fo Re Tr (s
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Non-qualifed Stock Option (right to buy)	$4.563	12/10/2003		M	V		15,000 (2)	01/02/2002	01/02/2011	Common Stock, Par Value $0.001	15,000	$16.5645	

Explanation of Responses:

1. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.
2. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Act of 1934, as amended.

Remarks:

Charles Gregory Vontz 12/11/2003

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1 (b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	Director: 10% Owner; X Officer (give title below): Chief Operating Officer; Other (specify below)
(Last) (First) (Middle): 3290 W. BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 11/28/2003	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction (s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	11/28/2003		J		801 (1)	A	$10.302	21,782	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Numbe of derivative Securities Beneficia Owned Following Reported Transacti (s) (Instr.
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		

Explanation of Responses:

1. Shares acquired through a qualified Section 423 Stock Purchase Plan.

Remarks:

Charles Gregory Vontz 12/01/2003

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

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SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1 (b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer
VONTZ CHARLES GREGORY	CONNETICS CORP [CNCT]	(Check all applicable)
(Last) (First) (Middle)	3. Date of Earliest Transaction (Month/Day/Year)	Director / 10% Owner
3290 WEST BAYSHORE RD.	09/10/2003	X Officer (give title below) / Other (specify below)
(Street)	4. If Amendment, Date of Original Filed (Month/Day/Year)	Chief Operating Officer
PALO ALTO CA 94303		6. Individual or Joint/Group Filing (Check Applicable Line)
(City) (State) (Zip)		X Form filed by One Reporting Person / Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	09/10/2003		M		13,541	A	$4.5625	34,522	D	
Common Stock, Par Value $0.001	09/10/2003		S		13,451 (1)	D	$17.4949	20,981	D	
Common Stock, Par Value $0.001	09/10/2003		M		1,459	A	$4.5625	22,440	D	
Common Stock, Par Value $0.001	09/10/2003		S		1,459 (2)	D	$17.4949	20,981	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. of de Se Be Ow Fo Re Tr (s
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		

Incentive Stock Option (right to buy)	$4.5625	09/10/2003		M		13,541 (3)	09/10/2003	01/02/2011	Common Stock, Par Value $0.001	13,541	$0
Non-qualified Stock Option (right to buy)	$4.6525	09/10/2003		M		1,459 (4)	09/10/2003	01/02/2011	Common Stock, Par Value $0.001	1,459	$0

Explanation of Responses:

1. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.
2. Sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.
3. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.
4. Exercise and sale pursuant to plan adopted under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended.

/s/ Katrina J. Church attorney in fact for Charles Gregory Vontz — 09/11/2003

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

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SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	January 31, 2008
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1 (b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
VONTZ CHARLES GREGORY (Last) (First) (Middle) (Street) (City) (State) (Zip)	CONNETICS CORP [CNCT] 3. Date of Earliest Transaction (Month/Day/Year) 05/30/2003 4. If Amendment, Date of Original Filed (Month/Day/Year)	Director ☐ 10% Owner X Officer (give title below) ☐ Other (specify below) Chief Operating Officer 6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person ☐ Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction (s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	05/30/2003		J		1261 (1)	A	10.3020	20981	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Numbe of derivative Securities Beneficia Owned Following Reported Transacti (s) (Instr.
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		

Explanation of Responses:

1 . Shares acquired through a qualified Section 423 Stock Purchase Plan.

/s/ Charles Gregory Vontz — 06/02/2003

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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OMB APPROVAL
OMB Number: 3235-0287
Expires: January 31, 2005
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 4

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1(b).

1. Name and Address of Reporting Person*

Vontz, Charles Gregory

(Last) (First) (Middle)

3290 W. Bayshore Road

(Street)

Palo Alto, CA 94303

(City) (State) (Zip)

2. Issuer Name and Ticker or Trading Symbol

Connetics Corporation (CNCT)

3. I.R.S. Identification Number of I Person, if an entity *(Voluntary)*

4. Statement for Month/Day/Year

1/2/03

5. If Amendment, Date of Original *(Month/Day/Year)*

6. Relationship of Reporting Person(s) to Issuer *(Check All Applicable)*

☐ Director ☐ 10% Owner

☒ Officer *(give title below)*

☐ Other *(specify below)*

Chief Operating Officer

7. Individual or Joint/Group Filing *(Check Applicable Line)*

☒ Form Filed by One Reporting

☐ Form Filed by More than One Reporting Person

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* instruction 4(b)(v).

Table I — Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security *(Instr. 3)*	2. Transaction Date *(Month/Day/Year)*	2A. Deemed Execution Date, if any *(Month/Day/Year)*	3. Transaction Code *(Instr. 8)*		4. Securities Acquired (A) or Disposed of (D) *(Instr. 3, 4 and 5)*			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) *(Instr. 3 and 4)*	6. Ownership Form: Direct (D) or Indirect (I) *(Instr. 4)*	7. Nature of Indirect Beneficial Ownership *(Instr. 4)*
			Code	V	Amount	(A) or (D)	Price			

Page 2

Table II — Derivative Securities Acquired, Disposed of, or Beneficially Owned
(*e.g.*, puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security *(Instr. 3)*	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date *(Month/Day/Year)*	3A. Deemed Execution Date, if any *(Month/Day/Year)*	4. Transaction Code *(Instr. 8)*		5. Number of Derivative Securities Acquired (A) or Disposed of (D) *(Instr. 3, 4 and 5)*	
				Code	V	(A)	(D)
Common Stock, Par Value $0.0001	$12.45	1/2/03		A		125,000 (1)	

Table II — Derivative Securities Acquired, Disposed of, or Beneficially Owned — Continued
(*e.g.*, puts, calls, warrants, options, convertible securities)

6. Date Exercisable and Expiration Date *(Month/Day/Year)*		7. Title and Amount of Underlying Securities *(Instr. 3 and 4)*		8. Price of Derivative Security *(Instr. 5)*	9. Number of Derivative Securities Beneficially Owned Following Reported Transaction(s) *(Instr. 4)*	10. Ownership Form of Derivative Security: Direct (D) or Indirect (I) *(Instr. 4)*	11. Nature of Indirect Beneficial Ownership *(Instr. 4)*
Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
	1/2/13	Common Stock, Par Value $0.001	125,000			D	

Explanation of Responses:

(1)- The options were granted under the Connetics Corporation 2000 Stock Plan and are exercisable at the rate of 1/4 on the one year anniversary and 1/48 per month thereafter.

/s/ Charles G. Vontz — 1/6/03

**Signature of Reporting Person — Date

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations. *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

FORM 4

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1(b).

(Print or Type Responses)

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(f) of the Investment Company Act of 1940

OMB APPROVAL
OMB Number: 3235-0287
Expires: December 31, 2001
Estimated average burden hours per response 0.5

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	6. Relationship of Reporting Person(s) to Issuer (Check all applicable)
Vontz, Charles Gregory (Last) (First) (Middle) 3290 West Bayshore Road (Street) Palo Alto, CA 94303 (City) (State) (Zip)	Connetics Corporation (CNCT) 3. I.R.S. Identification Number of Reporting Person, if an entity (Voluntary) 4. Statement for Month/Year: July 2002 5. If Amendment, Date of Original (Month/Year)	___ Director ___ 10% Owner X Officer (give title below) ___ Other (specify below) Chief Operating Officer 7. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person ___ Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned at End of Month (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
		Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	07/29/02	M		13,125	A	$4.5630		D	
Common Stock, Par Value $0.001	07/29/02	S		13,125	D	$10.4051		D	
Common Stock, Par Value $0.001	07/29/02	M		11,875	A	$4.5625		D	
Common Stock, Par Value $0.001	07/29/02	S		11,875	D	$10.4051	17,682	D	

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly. *If the form is filed by more than one reporting person, *see* Instruction 4(b)(v).

Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB control number.

(Over)

SEC 1474 (3-99)

FORM 4 (continued)

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned
(e.g. puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4, and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Underlying Securities (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned at End of Month (Instr. 4)	10. Ownership Form of Derivative Security: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Non-Qualified Stock Option (right to buy)	$4.5630	07/29/02	M			13,125 (1)		10/12/10	Common Stock, Par Value $0.001	13,125		16,875	D	
Non-Qualified Stock Option (right to buy)	$4.5630	07/29/02	M			11,875 (1)		01/02/11	Common Stock, Par Value $0.001	11,875		42,813	D	

Explanation of Responses:

See continuation page(s) for footnotes

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations. *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

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Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

**Signature of Reporting Person

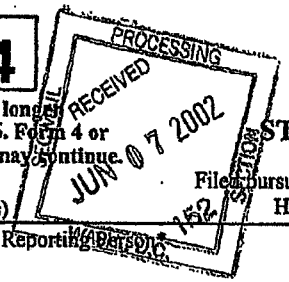
8/5/02
Date

(1) The options were granted under the Connetics Corporation 2000 Stock plan and are exercisable 25% after 12 months and monthly thereafter.

FORM 4

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1(b).

(Print or Type Responses)



UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(f) of the Investment Company Act of 1940

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	December 31, 2001
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	6. Relationship of Reporting Person(s) to Issuer (Check all applicable)
Vontz, Charles Gregory	**Connetics Corporation (CNCT)**	___ Director ___ 10% Owner X Officer (give title below) ___ Other (specify below) **Chief Operating Officer**
(Last) (First) (Middle) **3290 West Bayshore Road** (Street) **Palo Alto, CA 94303** (City) (State) (Zip)	3. I.R.S. Identification Number of Reporting Person, if an entity (Voluntary)	4. Statement for Month/Year **May 2002**
	5. If Amendment, Date of Original (Month/Year)	7. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person ___ Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned at End of Month (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
		Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	**05/31/02**	**J**	**V**	**3,026 (1)**	**A**	**$4.1969**	**17,682**	**D**	

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly. *If the form is filed by more than one reporting person, *see* Instruction 4(b)(v).

Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB control number.

FORM 4 (continued)

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned
(*e.g.* puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4, and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Underlying Securities (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned at End of Month (Instr. 4)	10. Ownership Form of Derivative Security: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				

Explanation of Responses:

See continuation page(s) for footnotes

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations. *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

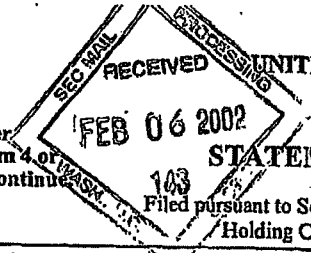
Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

**Signature of Reporting Person

6/4/02
Date

(1) Shares acquired through a qualified Section 423 Stock Purchase Plan.

FORM 4



UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	December 31, 2001
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1(b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(f) of the Investment Company Act of 1940

(Print or Type Responses)

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	6. Relationship of Reporting Person(s) to Issuer (Check all applicable)
Vontz, Charles Gregory (Last) (First) (Middle) 3290 West Bayshore Road (Street) Palo Alto, CA 94303 (City) (State) (Zip)	Connetics Corporation (CNCT) 3. I.R.S. Identification Number of Reporting Person, if an entity (Voluntary) 4. Statement for Month/Year: January 2002 5. If Amendment, Date of Original (Month/Year)	___ Director ___ 10% Owner X Officer (give title below) ___ Other (specify below) Chief Operating Officer 7. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person ___ Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned at End of Month (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
		Code	V	Amount	(A) or (D)	Price			

31566738

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly. *If the form is filed by more than one reporting person, *see* Instruction 4(b)(v).

Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB control number.

FORM 4 (continued)

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned
(e.g. puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4, and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Underlying Securities (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned at End of Month (Instr. 4)	10. Ownership Form of Derivative Security: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4
			Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Incentive Stock Option (right to buy)	**$11.9000**	**01/01/02**	**A**	V	**10,788 (1)**			**01/01/12**	**Common Stock, Par Value $0.001**	**10,788**		**10,788**	**D**	
Non-Qualified Stock Option (right to buy)	**$11.9000**	**01/01/02**	**A**	V	**74,212 (1)**			**01/01/12**	**Common Stock, Par Value $0.001**	**74,212**		**74,212**	**D**	

Explanation of Responses:

See continuation page(s) for footnotes

**Signature of Reporting Person

1/25/02
Date

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations.
See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

(1) The options were granted under the Connetics Corporation 2000 Stock plan and are exercisable to the extent of 1/4 on the one year anniversary and 1/48 per month thereafter.

FORM 4

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1(b).

(Print or Type Responses)

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

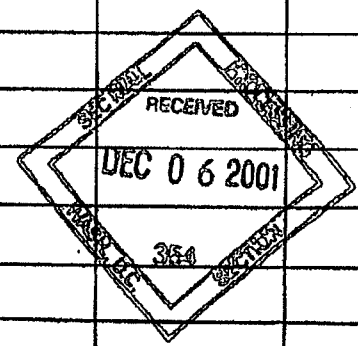
Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(f) of the Investment Company Act of 1940

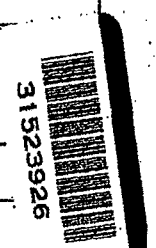
OMB APPROVAL	
OMB Number:	3235-0287
Expires:	December 31, 2001
Estimated average burden hours per response	0.5

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	6. Relationship of Reporting Person(s) to Issuer (Check all applicable)
Vontz, Charles Gregory (Last) (First) (Middle) 3400 West Bayshore Road (Street) Palo Alto, CA 94303 (City) (State) (Zip)	Connetics Corporation (CNCT) 3. I.R.S. Identification Number of Reporting Person, if an entity (Voluntary) 4. Statement for Month/Year: November 2001 5. If Amendment, Date of Original (Month/Year)	___ Director ___ 10% Owner X Officer (give title below) ___ Other (specify below) Chief Operating Officer 7. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person ___ Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned at End of Month (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
		Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	11/30/01	P		228 (1)	A	$4.1970	14,656	D	





Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly. *If the form is filed by more than one reporting person, *see* Instruction 4(b)(v).

Potential persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB control number.

(Over)

SEC 1474 (3-99)

FORM 4 (continued)

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned
(*e.g.* puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4, and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Underlying Securities (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned at End of Month (Instr. 4)	10. Ownership Form of Derivative Security: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				

Explanation of Responses:

See continuation page(s) for footnotes

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations.
See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

Potential persons who are to respond to the collection of information contained in this form are not

****Signature of Reporting Person** — **Date** 12/5/01

(1) Shares acquired through a qualified Section 423 Stock Purchase Plan.

EXHIBIT 24

SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	February 28, 2011
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1(b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name **and** Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
KROCHMAL LINCOLN	CONNETICS CORP [CNCT]	Director: 10% Owner
(Last) (First) (Middle)	3. Date of Earliest Transaction (Month/Day/Year)	X Officer (give title below): EVP Research & Product Dev.
3160 PORTER DRIVE	02/01/2006	Other (specify below)
(Street)	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line)
PALO ALTO CA 94304		X Form filed by One Reporting Person
(City) (State) (Zip)		Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock, Par Value $0.001	02/01/2006		A		60,860	A	$0.001	60,860	D	

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				

Explanation of Responses:

Remarks:

Lincoln Krochmal 02/03/2006

** Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	February 28, 2011
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1 (b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name **and** Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
KROCHMAL LINCOLN	CONNETICS CORP [CNCT]	Director: — 10% Owner: — Officer (give title below): X — Other (specify below): — EVP Research & Product Dev.
(Last) (First) (Middle): 3290 WEST BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 01/18/2005	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9.
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Non-Qualified Stock Option (right to buy)	$23.35	01/18/2005		A		40,183 (1)		01/18/2006	01/18/2015	Common Stock, Par Value $0.001	40,183	$23.35	
Incentive Stock Option (right to buy)	$23.35	01/18/2005		A		4,817 (1)		01/18/2006	01/18/2015	Common Stock, Par Value $0.001	4,817	$23.35	

Explanation of Responses:

1. The ISO/NQ options were granted under the Connetics Corporation 2000 Stock Plan and are exercisable at the rate of 25% on the one year anniversary and 1/48

per month thereafter.

Remarks:

Lincoln Krochmal	01/19/2005
** Signature of Reporting Person	Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	February 28, 2011
Estimated average burden hours per response	0.5

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1 (b).

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
KROCHMAL LINCOLN	CONNETICS CORP [CNCT]	Director: — 10% Owner: — Officer (give title below): X Other (specify below): — EVP Research & Product Dev.
(Last) (First) (Middle): 3290 W. BAYSHORE ROAD	3. Date of Earliest Transaction (Month/Day/Year): 01/05/2004	
(Street): PALO ALTO CA 94303	4. If Amendment, Date of Original Filed (Month/Day/Year): 01/05/2004	6. Individual or Joint/Group Filing (Check Applicable Line): X Form filed by One Reporting Person; Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. of d S B O F R T (s
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares		
Common Stock, Par Value $0.001	$18.05	01/05/2004		A		25,000 (1)		01/05/2005	01/05/2014	Common Stock, Par Value $0.001	25,000	$18.05	

Explanation of Responses:

1. The options were granted under the Connetics Corporation 2000 Stock Plan and are exercisable at the rate of 1/4 on the one year anniversary and 1/48 per month thereafter.

Remarks:

Katrina J. Church attorney in fact for Lincoln Krochmal — 01/12/2004

** Signature of Reporting Person | Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 4

FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0287
Expires:	February 28, 2011
Estimated average burden hours per response	0.5

☐ Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. *See* Instruction 1(b).

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Issuer Name and Ticker or Trading Symbol	5. Relationship of Reporting Person(s) to Issuer (Check all applicable)
KROCHMAL LINCOLN	CONNETICS CORP [CNCT]	Director / 10% Owner / X Officer (give title below) / Other (specify below)
(Last) (First) (Middle)	3. Date of Earliest Transaction (Month/Day/Year)	EVP Research & Product Dev.
3290 W. BAYSHORE ROAD	01/02/2004	
(Street)	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line)
PALO ALTO CA 94303		X Form filed by One Reporting Person / Form filed by More than One Reporting Person
(City) (State) (Zip)		

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction (s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares			
Common Stock, Par Value $0.001	$18.05	01/02/2004		A		25,000 (1)		01/02/2005	01/02/2014	Common Stock, Par Value $0.001	25,000	$18.05	125,000	D

Explanation of Responses:

1. The options were granted under the Connetics Corporation 2000 Stock Plan and are exercisable at the rate of 1/4 on the one year anniversary and 1/48 per month thereafter.

Remarks:

Lincoln Krochmal 01/05/2004

** Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 4 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

SEC Form 3

FORM 3

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

OMB APPROVAL	
OMB Number:	3235-0104
Expires:	February 28, 2011
Estimated average burden hours per response	0.5

INITIAL STATEMENT OF BENEFICIAL OWNERSHIP OF SECURITIES

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person*	2. Date of Event Requiring Statement (Month/Day/Year)	3. Issuer Name and Ticker or Trading Symbol
KROCHMAL LINCOLN (Last) (First) (Middle) 3290 W. BAYSHORE RD. (Street) PALO ALTO CA 94303 (City) (State) (Zip)	09/18/2003	CONNETICS CORP [CNCT]

4. Relationship of Reporting Person(s) to Issuer (Check all applicable)	5. If Amendment, Date of Original Filed (Month/Day/Year)
Director — 10% Owner X Officer (give title below) — Other (specify below) EVP, Research & Prod. Dev.	6. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by One Reporting Person Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Beneficially Owned

1. Title of Security (Instr. 4)	2. Amount of Securities Beneficially Owned (Instr. 4)	3. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	4. Nature of Indirect Beneficial Ownership (Instr. 5)

Table II - Derivative Securities Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 4)	2. Date Exercisable and Expiration Date (Month/Day/Year)		3. Title and Amount of Securities Underlying Derivative Security (Instr. 4)		4. Conversion or Exercise Price of Derivative Security	5. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	6. Nature of Indirect Beneficial Ownership (Instr. 5)
	Date Exercisable	Expiration Date	Title	Amount or Number of Shares			
Incentive Stock Option (right to buy)	03/18/2004	09/18/2013	Common Stock, par value $0.001	101,568 (1)	17.07	D	
Non-qualified Stock Option (right to buy)	03/18/2004	09/18/2013	Common Stock, par value $0.001	23,432 (1)	17.07	D	

Explanation of Responses:

1. The options were granted under the 2000 Stock Plan and are exercisable 12.5% after 6 months and monthly thereafter.

Remarks:

Katrina J. Church as Attorney-in-Fact for Lincoln Krochmal — 09/24/2003

** Signature of Reporting Person — Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, *see* Instruction 5 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

EXHIBIT 25

CONNETICS CORP

3400 W BAYSHORE RD
PALO ALTO, CA 94303
415. 843.2800

DEFR14A

DEFINITIVE PROXY STATEMENT – REVISED
Filed on 04/21/2006
File Number 000–27406

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of the Securities Exchange Act of 1934 (Amendment No. 1)

Filed by the Registrant ☒
Filed by a Party other than the Registrant ☐
Check the appropriate box:

☐ Preliminary Proxy Statement
☐ **Confidential, for Use of the Commission Only (as permitted by Rule 14a–6(e)(2))**
☒ Definitive Proxy Statement
☐ Definitive Additional Materials
☐ Soliciting Material Pursuant to §240.14a–12

Connetics Corporation

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

☒ No fee required.
☐ Fee computed on table below per Exchange Act Rules 14a–6(i)(1) and 0–11.

(1) Title of each class of securities to which transaction applies:

(2) Aggregate number of securities to which transaction applies:

(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0–11 (set forth the amount on which the filing fee is calculated and state how it was determined):

(4) Proposed maximum aggregate value of transaction:

(5) Total fee paid:

☐ Fee paid previously with preliminary materials.

☐ Check box if any part of the fee is offset as provided by Exchange Act Rule 0–11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

(1) Amount Previously Paid:

(2) Form, Schedule or Registration Statement No.:

(3) Filing Party:

(4) Date Filed:

STOCK OWNERSHIP

Who are the largest owners of Connetics stock, and how much stock do our directors and executive officers own?

The following table sets forth certain information we know with respect to the beneficial ownership of our common stock as of March 24, 2006 by (a) all persons who are beneficial owners of more than five percent of our common stock, (b) each director and nominee, (c) each of our executive officers named in the Summary Compensation Table below, and (d) all director nominees, current directors and executive officers as a group.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC and generally includes voting or investment power with respect to securities. Percentage ownership is based on 34,224,303 shares of common stock outstanding at March 24, 2006, which excludes 3,357,307 treasury shares. Except as indicated otherwise in the footnotes below, and subject to community property laws where applicable, we believe that the persons named in the table below have sole voting and investment power with respect to all shares of common stock shown.

Name	Number of Shares	Percentage of Shares Outstanding	Footnote(s)
Wellington Management Company, LLP 75 State Street Boston, Massachusetts 02109	2,670,563	7.8%	(1)
Barclays Global Investors, N.A. Barclays Global Fund Advisors Barclays Bank PLC Barclays Capital Securities Limited 45 Fremont Street San Francisco, CA 94105	2,039,830	5.96%	(2)
Capital Research and Management Company and SMALLCAP World Fund, Inc. 333 South Hope Street Los Angeles, CA 90071	2,000,000	5.84%	(3)
Thomas G. Wiggans	1,526,247	4.30%	(4)
C. Gregory Vontz	737,707	2.12%	(5)
John L. Higgins	603,625	1.74%	(6)
G. Kirk Raab	492,790	1.42%	(7)
Katrina J. Church	400,054	1.16%	(8)
Thomas D. Kiley	258,615	*	(9)
Lincoln Krochmal, M.D.	214,193	*	(10)
John C. Kane	149,939	*	(11)
Denise M. Gilbert, Ph.D.	61,111	*	(12)
Leon E. Panetta	53,264	*	(13)
R. Andrew Eckert	53,611	*	(14)
Carl B. Feldbaum	30,000	*	(15)
David E. Cohen, M.D.	0	*	
All directors and officers as a group (26 persons)	5,372,569	13.91%	(16)

* Less than 1%.

(1) As reported on a Schedule 13G/ A filed with the SEC on or about December 30, 2005. Represents 2,670,563 shares as to which Wellington Management Company, LLP has shared dispositive power, and 2,538,863 shares as to which Wellington Management Company, LLP has shared voting power, with the unnamed beneficial owners, who are clients of Wellington Management Company, LLP.

(2) As reported on a Schedule 13G/ A filed with the SEC on or about December 31, 2004 by Barclays Global Investor, N.A. and a group of affiliated entities. According to the Schedule 13G/ A, the following entities have sole voting power with respect to an aggregate of 1,885,547 shares and dispositive power with respect to an aggregate of 2,039,830 shares held in trust accounts for the economic benefit of the beneficiaries of those accounts: Barclays Global Investors, N.A., (828,606 shares, voting power and 982,889 shares, dispositive power); Barclays Global Fund Advisors (707,844 shares); Barclays Bank PLC (338,611 shares); and Barclays Capital Securities Limited (10,486 shares).

(3) As reported on a Schedule 13G filed with the SEC on or about December 30, 2005. Represents 2,000,000 shares as to which Capital Research and Management Company, an investment adviser registered under Section 203 of the Investment Advisers Act of 1940 has sole dispositive and voting power. Capital Research and Management Company is deemed to be the beneficial owner of and as a result is acting as investment advisor to various investment companies registered under Section 8 of the Investment Company Act of 1940. SMALLCAP World Fund, Inc., an investment company registered under the Investment Company Act of 1940, which is advised by Capital Research and Management Company, is the beneficial owner of 2,000,000 shares.

(4) Mr. Wiggans' total includes options to purchase 1,244,275 shares of common stock that will be exercisable on or before May 23, 2006. Also includes 10,490 shares held by Mr. Wiggans' wife, and 12,486 shares held in trust for Mr. Wiggans' children. Mr. Wiggans disclaims beneficial ownership of the shares held in trust.

(5) Mr. Vontz's total includes options to purchase 608,887 shares of common stock that will be exercisable on or before May 23, 2006.

(6) Mr. Higgins' total includes options to purchase 468,256 shares of common stock that will be exercisable on or before May 23, 2006. Also includes 250 shares of common stock held by Mr. Higgins' wife.

(7) Mr. Raab's total includes options to purchase 474,950 shares of common stock that will be exercisable on or before May 23, 2006.

(8) Ms. Church's total includes options to purchase 346,218 shares of common stock that will be exercisable on or before May 23, 2006.

(9) Mr. Kiley's total includes options to purchase 77,500 shares of common stock that will be exercisable on or before May 23, 2006. Also includes 167,365 shares held in the Thomas D. and Nancy L.M. Kiley Revocable Trust under Agreement dated August 7, 1981, and 10,000 shares held in The Kiley Family Partnership of which Mr. Kiley is a trustee, and as to 7,500 of which Mr. Kiley disclaims beneficial ownership.

(10) Dr. Krochmal's total includes options to purchase 153,333 shares of common stock that will be exercisable on or before May 23, 2006.

(11) Mr. Kane's total includes options to purchase 122,500 shares of common stock that will be exercisable on or before May 23, 2006.

(12) Dr. Gilbert's total includes options to purchase 60,000 shares of common stock that will be exercisable on or before May 23, 2006.

(13) Mr. Panetta's total includes options to purchase 45,000 shares of common stock that will be exercisable on or before May 23, 2006.

(14) Mr. Eckert's total includes options to purchase 52,500 shares of common stock that will be exercisable on or before May 23, 2006.

(15) Mr. Feldbaum's total includes options to purchase 30,000 shares of common stock that will be exercisable on or before May 23, 2006.

(16) See footnotes 4 through 15. The total includes options to purchase an aggregate of 4,395,829 shares of common stock that will be exercisable on or before May 23, 2006 by all of the officers and directors as a group.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our directors and certain executive officers, and any person who beneficially owns more than 10% of our common stock, to file reports of their holdings and transactions in Connetics stock with the SEC. Based on our records and other information, including a review of the copies of those reports furnished to us and written representations that no other reports were required to be filed, we believe that all of our directors and executive officers complied during 2005 with the filing requirements under Section 16(a), with one exception, which resulted from an administrative error on the part of the Company. As a result, the following outside directors who automatically received stock options on April 22, 2005 when they were re–elected to the Board, did not file reports with the SEC until May 17, 2005: Dr. Barkas, Dr. Bauer, Mr. Eckert, Dr. Gilbert, Mr. Kane, Mr. Kiley, Mr. Panetta, and Mr. Raab. Based solely on a review of copies of reports furnished to us, we believe that the beneficial owners of more than 10% of our common stock timely complied with all filing requirements under Section 16(a) for the year ended December 31, 2005.

CORPORATE GOVERNANCE

Our Commitment to Good Corporate Governance

We believe that good corporate governance and an environment of the highest ethical standards are important for Connetics to achieve business success and to create value for our stockholders. We continuously review our corporate governance practices in view of the Sarbanes–Oxley Act of 2002, rules of the SEC and Nasdaq listing rules. We also compare and conform as needed our governance practices with those identified as best practices by various authorities and other public companies. As a result, we continue to evaluate and strengthen the corporate governance processes at Connetics.

Management Executive Committee

The management Executive Committee has responsibility for the overall direction, strategy and operations of Connetics, including, among other things, corporate financial performance, commercial performance, research, development and product operations performance, and employee development performance. The six members of the management Executive Committee hold the following positions at Connetics:

- Chief Executive Officer,
- President and Chief Operating Officer,
- Executive Vice President, Finance and Corporate Development, and Chief Financial Officer,
- Executive Vice President, General Counsel and Secretary,
- Executive Vice President, Research and Product Development, and
- Senior Vice President, Technical Operations.

Board Meetings and Committees

While Connetics' executives are responsible for our daily operations, the Board manages our corporate resources, and is responsible for establishing broad corporate policies and for overseeing the overall performance of Connetics and management. The Board reviews significant developments affecting Connetics and acts on matters requiring Board approval, and reviews our corporate governance policies and practices. This review includes comparison of our current policies and practices to those mandated by legislation and regulation, including the Sarbanes–Oxley Act of 2002, regulations proposed or adopted by the SEC, and Nasdaq listing standards. This review also includes an assessment of policies and practices

EXHIBIT 26

OFFICE OF NEW DRUGS

NDAs: Filing Review Issues

CONTENTS

PURPOSE

- This MAPP establishes procedures for identifying review issues during the filing review of all original NDA applications and efficacy supplements within the Center for Drug Evaluation and Research (CDER) and outlines the procedures for informing the applicant about these issues. It does not apply to labeling supplements that contain clinical data.

BACKGROUND

- On June 12, 2002, the President signed the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, which includes the Prescription Drug User Fee Amendments of 2002 (PDUFA III). In conjunction with the June 2002 reauthorization of PDUFA, FDA agreed to meet specific performance goals (PDUFA Goals). The PDUFA Goals outline the basic requirements for first cycle review performance, including applicant notification of issues identified during the filing review.

- The June 2002 reauthorization of PDUFA performance goals directed FDA to "report substantive deficiencies identified in the initial filing review to the sponsor by letter, telephone conference, facsimile, secure e-mail, or other expedient means."

REFERENCES

- *PDUFA Reauthorization Performance Goals and Procedures*, an enclosure to a letter dated June 4, 2002, from the Secretary of Health and Human Services, Tommy Thompson, to Congress, available at http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html

- FDA/CDER guidance for industry on *Refusal to File*

DEFINITION

- **Filing review issues:** Substantive deficiencies or concerns identified by the review team during the initial filing review for an NDA or efficacy supplement that appear to have been inadequately addressed in the application and merit particular attention during the review process. These issues may have significant impact on the Agency's ability to complete the review of the application or approve the application or parts of the application. Filing review issues are distinct from application deficiencies that serve as the basis for a Refusal to File action. Filing review issues pertain only to applications that have been filed.

POLICY

- Any filing review issues identified during the filing review will be communicated to the applicant no later than 14 calendar days after the 60-day filing date.
- If the review team does not identify any filing review issues, the applicant will be informed of this fact no later than 14 calendar days after the 60-day filing date.
- This MAPP applies only to original NDA applications and original efficacy supplements. It does not apply to labeling supplements that contain clinical data.

PROCEDURES

- **Identification of Filing Review Issues:** During the initial filing review of a newly submitted original NDA or efficacy supplement, any issues that may meet the definition of a filing review issue should be identified and discussed within the review team (e.g., at a 45-day filing meeting). The review team can request a response from the applicant on any number or none of the identified issues.
- **Communication of Filing Review Issues to Applicant:** All filing review issues identified by the review team will be conveyed to the applicant in a single communication, which will include the Agency's expectations for applicant responses, if any. This communication may be by letter, telephone conference, facsimile, secure e-mail, or other expedient means, and should be made within the specified time frame.
- **Documentation of Filing Review Issues:** Communication of filing review issues to the applicant will be documented in writing and archived using standard CDER processes.

RESPONSIBILITIES

Review Team Members will:

- Identify any potential filing review issues during the filing review and inform the other members of the review team about these issues at or before the filing meeting.
- For each filing review issue, determine whether to request a response from the applicant.

Team Leaders,
Chiefs, Project Management Staff,
and Review Division Directors will:

- Provide guidance to the review team about identifying potential filing review issues and distinguishing any internal review discussion points that do not meet the definition of filing review issues.
- Determine the appropriateness of the filing review issues to be conveyed to the applicant.

Review Division Project Management Staff will:

- Convey and/or confirm conveyance of filing review issues, or lack thereof, to the applicant within the designated time frame, including standard language on the preliminary nature of these findings.
- Document in writing conveyance of filing review issues, or lack thereof, to applicant.

AUTHORITY

- Following discussion with the entire review team, if filing review issues are identified for multiple review disciplines, the Chief, Project Management Staff, or Review Division Director should authorize communication of that information to the applicant. If all filing review issues pertain to only one review discipline, the relevant review discipline team leader can authorize this communication.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

EXHIBIT 27

PHARMACOLOGY AND TOXICOLOGY

DISTRIBUTION OF FINAL REPORTS FROM THE CARCINOGENICITY ASSESSMENT COMMITTEE (CAC) AND EXECUTIVE CAC

CONTENTS

PURPOSE This MAPP establishes the policies and procedures by which the review divisions will provide sponsors with the final reports from the Carcinogenicity Assessment Committee (CAC) and the Executive CAC.

BACKGROUND

The CAC conducts a tertiary review of carcinogenicity studies in accordance with MAPP 7412.1, *Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive CAC*. The CAC review is of interest to sponsors who often request it from the review divisions.

The review divisions are responsible for all direct communication with sponsors, including recommendations from the CAC and Executive CAC. Since carcinogenicity studies submitted to the Center for Drug Evaluation and Research (CDER) should be reviewed by the CAC or Executive CAC, it is important that a mechanism to consistently communicate the CAC recommendations to sponsors is established. To achieve this objective, this guide describes the policy and procedures for releasing CAC final reports.

REFERENCES

- CDER MAPP 7412.1, *Management of CDER Carcinogenicity Assessment Committee (CAC) and Executive Committee.*

POLICY

- This policy applies to all final reports documenting the deliberations and recommendations of the CAC and the Executive CAC. Final reports should be provided to sponsors by the reviewing division upon written request by the sponsor.

- The recommendations in a CAC and Executive CAC final report of the carcinogenicity study results are advisory to the review divisions and office directors. These reports aid in the interpretation of the carcinogenicity study results and the potential relevance of the findings under the conditions of clinical use.

- The final reports generated by the CAC or Executive CAC on the dose selection and study design for proposed carcinogenicity protocols provide Center concurrence and/or recommendations for sponsors and are to be conveyed to the sponsor.

PROCEDURES

Releasing CAC and Executive CAC final reports:

- The review division should inform the sponsor when a proposed carcinogenicity protocol or study results will be reviewed by the CAC or Executive CAC. The final report for the protocol evaluation will be made available 75 days from the CDER receipt stamp date of the protocol.

- Upon written request, the full reports the CAC evaluation of the carcinogenicity study will be made available 30 days after the CAC meeting.

- The final report should be provided with a cover letter from the Division Director (or designate) clearly stating that the recommendations made by the CAC on carcinogenicity study evaluations are advisory and should not be interpreted by the sponsor as a measure of the approvability of their application.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

EXHIBIT 28

From Test Tube To Patient
A Special Report from *FDA Consumer* Magazine

Email this Page To a Friend

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

The path a drug travels from a lab to your medicine cabinet is usually long, and every drug takes a unique route. Often, a drug is developed to treat a specific disease. An important use of a drug may also be discovered by accident

For example, Retrovir (zidovudine, also known as AZT) was first studied as an anti-cancer drug in the 1960s with disappointing results. It wasn't until the 1980s that researchers discovered the drug could treat AIDS, and the Food and Drug Administration approved the drug, manufactured by GlaxoSmithKline, for that purpose in 1987.

Most drugs that undergo preclinical (animal) testing never even make it to human testing and review by the FDA.The drugs that do must undergo the agency's rigorous evaluation process, which scrutinizes everything about the drug--from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured.

Stages of Drug Developmentand Review

Investigational New Drug Application (IND)--The pharmaceutical industry sometimes provides advice to the FDA prior to submission of an IND. Sponsors--companies, research institutions, and other organizations that take responsibility for developing a drug--must show the FDA results of preclinical testing they've done in laboratory animals and what they propose to do for human testing. At this stage, the FDA decides whether it is reasonably safe for the company to move forward with testing the drug in humans.

Clinical Trials--Drug studies in humans can begin only after an IND is reviewed by the FDA and a local institutional review board (IRB). The board is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research.

IRBs approve the clinical trial protocols, which describe the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives, and other details. IRBs make sure the study is acceptable, that participants have given consent and are fully informed of their risks, and that researchers take appropriate steps to protect patients from harm.

Phase 1 studies are usually conducted in healthy volunteers. The goal here is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted. The number of subjects typically ranges from 20 to 80.

Phase 2 studies begin if Phase 1 studies don't reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the emphasis in Phase 2 is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually an inactive substance (placebo), or a different drug. Safety continues to be evaluated, and short-term side effects are studied. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300.

At the end of Phase 2, the FDA and sponsors try to come to an agreement on how the large-scale studies

in Phase 3 should be done. How often the FDA meets with a sponsor varies, but this is one of two most common meeting points prior to submission of a new drug application. The other most common time is pre-NDA--right before a new drug application is submitted.

Phase 3 studies begin if evidence of effectiveness is shown in Phase 2. These studies gather more information about safety and effectiveness, studying different populations and different dosages and using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people.

Postmarketing study commitments, also called Phase 4 commitments, are studies required of or agreed to by a sponsor that are conducted after the FDA has approved a product for marketing. The FDA uses postmarketing study commitments to gather additional information about a product's safety, efficacy, or optimal use.

New Drug Application (NDA)--This is the formal step a drug sponsor takes to ask that the FDA consider approving a new drug for marketing in the United States. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

When an NDA comes in, the FDA has 60 days to decide whether to file it so that it can be reviewed. The FDA can refuse to file an application that is incomplete. For example, some required studies may be missing. In accordance with the Prescription Drug User Fee Act (PDUFA), the FDA's Center for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of NDAs for standard drugs no later than 10 months after the applications are received. The review goal is six months for priority drugs. (See "The Role of User Fees.")

There is also continuous interaction throughout the review process. For example, over roughly six years, the sponsor, Merck Research Laboratories of West Point, Pa., and the FDA had several face-to-face meetings and about 28 teleconferences regarding the asthma drug Singulair (montelukast sodium).

"It's the clinical trials that take so long--usually several years," says Sandra Kweder, M.D., deputy director of the Office of New Drugs in the CDER. "The emphasis on speed for FDA mostly relates to review time and timelines of being able to meet with sponsors during a drug's development," she says.

Reviewing Applications

Though FDA reviewers are involved with a drug's development throughout the IND stage, the official review time is the length of time it takes to review a new drug application and issue an action letter, an official statement informing a drug sponsor of the agency's decision.

Once a new drug application is filed, an FDA review team--medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts--evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. No drug is absolutely safe; all drugs have side effects. "Safe" in this sense means that the benefits of the drug appear to outweigh the risks.

The review team analyzes study results and looks for possible issues with the application, such as weaknesses of the study design or analyses. Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to make a decision.

Each reviewer prepares a written evaluation containing conclusions and recommendations about the application. These evaluations are then considered by team leaders, division directors, and office directors, depending on the type of application.

Reviewers receive training that fosters consistency in drug reviews, and good review practices remain a high priority for the agency.

Sometimes, the FDA calls on advisory committees made up of outside experts, who help the agency decide on drug applications. Whether an advisory committee is needed depends on many things.

"Some considerations would be if it's a drug that has significant questions, if it's the first in its class, or the first for a given indication," says Mark Goldberger, M.D., director of one of CDER's drug review offices. "Generally, FDA takes the advice of advisory committees, but not always," he says. "Their role is just that--

to advise."

Accelerated Approval

Traditional approval requires that clinical benefit be shown before approval can be granted. Accelerated approval is given to some new drugs for serious and life-threatening illnesses that lack satisfactory treatments. This allows an NDA to be approved before measures of effectiveness that would usually be required for approval are available.

Instead, less traditional measures called surrogate endpoints are used to evaluate effectiveness. These are laboratory findings or signs that may not be a direct measurement of how a patient feels, functions, or survives, but are considered likely to predict benefit. For example, a surrogate endpoint could be the lowering of HIV blood levels for short periods of time with anti-retroviral drugs.

Gleevec (imatinib mesylate), an oral treatment for patients with a life-threatening form of cancer called chronic myeloid leukemia (CML), received accelerated approval. The drug was also approved under the FDA's orphan drug program, which gives financial incentives to sponsors for manufacturing drugs that treat rare diseases. Gleevec blocks enzymes that play a role in cancer growth. The approval was based on results of three large Phase 2 studies, which showed the drug could substantially reduce the level of cancerous cells in the bone marrow and blood.

The sponsor, Novartis Pharmaceuticals Corp. of East Hanover, N.J., submitted the IND in April 1998. The FDA received the NDA in February 2001, and the drug was approved two-and-a-half months later in May 2001. Novartis has made commitments to conduct studies that confirm Gleevec's clinical benefit, such as increased progression-free survival in the treatment of CML.

Most drugs to treat HIV have been approved under accelerated approval provisions, with the company required to continue its studies after the drug is on the market to confirm that its effects on virus levels are maintained and that it ultimately benefits the patient. Under accelerated approval rules, if studies don't confirm the initial results, the FDA can withdraw the approval.

Because premarket review can't catch all potential problems with a drug, the FDA continues to track approved drugs for adverse events through a postmarketing surveillance program.

Bumps in the Road

If the FDA decides that the benefits of a drug outweigh the risks, the drug will receive approval and can be marketed in the United States. But if there are problems with an NDA or if more information is necessary to make that determination, the FDA may decide that a drug is "approvable" or "not approvable."

A designation of approvable means that the drug can probably be approved, provided that some issues are resolved first. This might involve the sponsor and the FDA coming to a final agreement on what should go on the drug's labeling, for example. It could also involve more difficult issues, such as the adequacy of information on how people respond to various dosages of the drug.

A designation of "not approvable" describes deficiencies significant enough that it is not clear that approval can be obtained in the future, at least not without substantial additional data.

Common problems include unexpected safety issues that crop up or failure to demonstrate a drug's effectiveness. A sponsor may need to conduct additional studies--perhaps studies of more people, different types of people, or for a longer period of time.

Manufacturing issues are also among the reasons that approval may be delayed or denied. Drugs must be manufactured in accordance with standards called good manufacturing practices, and the FDA inspects manufacturing facilities before a drug can be approved. If a facility isn't ready for inspection, approval can be delayed. Any manufacturing deficiencies found would need to be corrected before approval.

"Sometimes a company may make a certain amount of a drug for clinical trials. Then when they go to scale up, they may lose a supplier or end up with quality control issues that result in a product of different chemistry," says the FDA's Kweder. "Sponsors have to show us that the product that's going to be marketed is the same product that they tested."

John Jenkins, M.D., director of CDER's Office of New Drugs, says, "It's often a combination of problems that prevent approval." Close communication with the FDA early on in a drug's development reduces the chance that an application will have to go through more than one cycle of review, he says. "But it's no guarantee."

The FDA outlines the justification for its decision in an action letter to the drug sponsor. When the action is either approvable or not approvable, CDER gives the sponsor a chance to meet with agency officials to discuss the deficiencies. At that point, the sponsor can choose to ask for a hearing, or correct any deficiencies and submit new information, or they can withdraw the application.

Drug Review Steps

1. Preclinical (animal) testing.
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. Phase 1 studies (typically involve 20 to 80 people).
4. Phase 2 studies (typically involve a few dozen to about 300 people).
5. Phase 3 studies (typically involve several hundred to about 3,000 people).
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug).
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or find it either "approvable" or "not approvable."

The Role of User Fees

Since the Prescription Drug User Fee Act (PDUFA) was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections. PDUFA has allowed the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process.

Under PDUFA, drug companies agree to pay fees that boost FDA resources, and the FDA agrees to time goals for its review of new drug applications. Along with supporting increased staff, drug user fees help the FDA upgrade resources in information technology. The agency has moved toward an electronic submission and review environment, now accepting more electronic applications and archiving review documents electronically.

The goals set by PDUFA apply to the review of original new human drug and biological applications, resubmissions of original applications, and supplements to approved applications. The second phase of PDUFA, known as PDUFA II, was reauthorized in 1997 and extended the user fee program through September 2002. PDUFA III, which extends to Sept. 30, 2007, was reauthorized in June 2002.

PDUFA III allows the FDA to spend some user fees to increase surveillance of the safety of medicines during their first two years on the market, or three years for potentially dangerous medications. It is during this initial period, when new medicines enter into wide use, that the agency is best able to identify and counter adverse side effects that did not appear during the clinical trials.

In addition to setting time frames for review of applications, PDUFA sets goals to improve communication and sets goals for specific kinds of meetings between the FDA and drug sponsors. It also outlines how fast the FDA must respond to requests from sponsors. Throughout a drug's development, the FDA advises sponsors on how to study certain classes of drugs, how to submit data, what kind of data are needed, and how clinical trials should be designed.

The Quality of Clinical Data

The Food and Drug Administration relies on data that sponsors submit to decide whether a drug should be approved. To protect the rights and welfare of people in clinical trials, and to verify the quality and integrity of data submitted, the FDA's Division of Scientific Investigations (DSI) conducts inspections of clinical investigators' study sites. DSI also reviews the records of institutional review boards to be sure they are fulfilling their role in patient protection.

"FDA investigators compare information that clinical investigators provided to sponsors on case report forms with information in source documents such as medical records and lab results," says Carolyn Hommel, a consumer safety officer in DSI.

DSI seeks to determine such things as whether the study was conducted according to the investigational plan, whether all adverse events were recorded, and whether the subjects met the inclusion/exclusion criteria outlined in the study protocol.

At the conclusion of each inspection, FDA investigators prepare a report summarizing any deficiencies. In cases where they observe numerous or serious deviations, such as falsification of data, DSI classifies the inspection as "official action indicated" and sends a warning letter or Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to the clinical investigator, specifying the deviations that were found.

The NIDPOE begins an administrative process to determine whether the clinical investigator should remain eligible to receive investigational products and conduct clinical studies.

CDER conducts about 300-400 clinical investigator inspections annually. About 3 percent are classified in this "official action indicated" category.

The FDA has established an independent Drug Safety Oversight Board (DSOB) to oversee the management of drug safety issues and communication to the public about the risks and benefits of medicines. The board's responsibilities include conducting timely and comprehensive evaluations of emerging drug safety issues, selecting drugs to be placed on a Drug Watch Web site for health professionals and patients, and ensuring that experts--both inside and outside of the FDA--give their perspectives to the agency. The first meeting of the DSOB was held in June 2005.

For More Information

Drug Safety Oversight Board Meetings
www.fda.gov/cder/drug/DrugSafety/DSOBmeetings/

EXHIBIT 29

Reviews Complete and Acceptable?

Much of the primary review process involves reviewer attempts to confirm and validate the sponsor's conclusion that a drug is safe and effective for its proposed use. The review is likely to involve a reanalysis or an extension of the analyses performed by the sponsor and presented in the NDA. For example, the medical reviewer may seek to reanalyze a drug's effectiveness in a particular patient subpopulation not analyzed in the original submission. Similarly, the reviewer may disagree with the sponsor's assessment of evaluable patients and seek to retest effectiveness claims based on the reviewer-defined patient populations.

There is also extensive communication between review team members. If a medical reviewer's reanalysis of clinical data produces results different from those of the sponsor, for example, the reviewer is likely to forward this information to the statistical reviewer with a request for a statistical reanalysis of the data. Likewise, the pharmacology reviewer may work closely with the statistical reviewer in evaluating the statistical significance of potential cancer-causing effects of the drug in long-term animal studies.

When the technical reviews are completed, each reviewer develops a written evaluation of the NDA that presents their conclusions and their recommendations on the application. The division director or office director then evaluates the reviews and recommendations and decides the action that the division will take on the application. The result is an action letter that provides an approval, approvable or non-approvable decision and a justification for that recommendation.

EXHIBIT 30

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

FINAL PRINTED LABELING

BenzaClin™ Topical Gel

Rx Only

(clindamycin - benzoyl peroxide gel)

Topical Gel: clindamycin (1%) as clindamycin phosphate, benzoyl peroxide (5%)
For Dermatological Use Only - Not for Ophthalmic Use
Reconstitute Before Dispensing

DESCRIPTION

BenzaClin™ Topical Gel contains clindamycin phosphate, (7(S)-chloro-7-deoxylincomycin-2-phosphate). Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

Chemically, clindamycin phosphate is ($C_{18}H_{34}ClN_2O_8PS$). The structural formula for clindamycin is represented below:

Insert
Clindamycin stucture
(see USP Dictionary of USAN and International Drug Names 1997 p. 173)

Clindamycin phosphate has molecular weight of 504.97 and its chemical name is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans- 4-propyl-L-2-pyrrolidinecarboxamido) - 1-thio-L- threo-alpha-D- galacto-octopyranoside 2-(dihydrogen phosphate).

BenzaClin Topical Gel also contains benzoyl peroxide, for topical use.
Chemically, benzoyl peroxide is ($C_{14}H_{10}O_4$). It has the following structural formula:

Insert
Benzoyl Peroxide stucture
(see USP Dictionary of USAN and International Drug Names 1997 p. 87)

Benzoyl peroxide has a molecular weight of 242.23.

Each gram of **BenzaClin Topical Gel** contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

CLINICAL PHARMACOLOGY

An *in vitro* percutaneous penetration study comparing **BenzaClin Topical Gel** and topical 1% clindamycin gel alone, demonstrated there was no statistical difference in penetration between the two drugs. Mean systemic bioavailability of topical clindamycin in **BenzaClin Topical Gel** is suggested to be less than 1%.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid. It is suggested that the lipophilic nature of benzoyl peroxide acts to concentrate the compound into the lipid-rich sebaceous follicle.

Microbiology:

The clindamycin and benzoyl peroxide components individually have been shown to have in vitro activity against *Propionibacterium acnes* an organism which has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product.

CLINICAL STUDIES

In two adequate and well controlled clinical studies of 758 patients, 214 used BenzaClin, 210 used benzoyl peroxide, 168 used clindamycin, and 166 used vehicle. BenzaClin applied twice daily for 10 weeks was significantly more effective than vehicle in the treatment of moderate to moderately severe facial acne vulgaris. Patients were evaluated and acne lesions counted at each clinical visit; weeks 2, 4, 6, 8 and 10. The primary efficacy measures were the lesion counts and the investigator's global assessment evaluated at week 10. Patients were instructed to wash the face with a mild soap, using only the hands. Fifteen minutes after the face was thoroughly dry, application was made to the entire face. Non-medicated make-up could be applied at one hour after the BenzaClin application. If a moisturizer was required, the patients were provided a moisturizer to be used as needed. Patients were instructed to avoid sun exposure. Percent reductions in lesion counts after treatment for 10 weeks in these two studies are shown below:

Study 1			
BenzaClin n=120	Benzoyl peroxide n=120	Clindamycin n=120	Vehicle n=120
Mean percent reduction in inflammatory lesion counts			
46%	32%	16%	+ 3%
Mean percent reduction in non-inflammatory lesion counts			
22%	22%	9%	+1%
Mean percent reduction in total lesion counts			
36%	28%	15%	0.2%

Study 2			
BenzaClin n=95	Benzoyl peroxide n=95	Clindamycin n=49	Vehicle n=48

Mean percent reduction in inflammatory lesion counts			
63%	53%	45%	42%
Mean percent reduction in non-inflammatory lesion counts			
54%	50%	39%	36%
Mean percent reduction in total lesion counts			
58%	52%	42%	39%

The BenzaClin group showed greater overall improvement than the benzoyl peroxide, clindamycin and vehicle groups as rated by the investigator.

INDICATIONS AND USAGE

BenzaClin Topical Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

BenzaClin Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

WARNINGS

ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTIBIOTIC- ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium Difficile* AND STOOL ASSAY FOR *Clostridium Difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS, AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vitro antagonism is not known.

Information for Patients: Patients using **BenzaClin Topical Gel** should receive the following information and instructions:

1. **BenzaClin Topical Gel** is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by physician.

4. Patients should report any signs of local adverse reactions to their physician.

5. **BenzaClin Topical Gel** may bleach hair or colored fabric.

6. Store refrigerated 2 to 8°C (36 to 46°F). Do not freeze. Discard any unused product after 2 months.

7. Before applying **BenzaClin Topical Gel** to affected areas wash the skin gently, then rinse with warm water and pat dry.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with BenzaClin Topical Gel. Clindamycin phosphate was not genotoxic in Salmonella typhimurium or in a rat micronucleus test. Clindamycin phosphate sulfoxide, an oxidative degradation product of clindamycin phosphate and benzoyl peroxide, was not clastogenic in a mouse micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonella typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with **BenzaClin Topical Gel** or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g BenzaClin Topical Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C:
Animal reproductive/developmental toxicity studies have not been conducted with BenzaClin Topical Gel or benzoyl peroxide. Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are no well-controlled trials in pregnant women treated with **BenzaClin Topical Gel**. It also is not known whether **BenzaClin Topical Gel** can cause fetal harm when administered to a pregnant woman.

Nursing Women: It is not known whether **BenzaClin Topical Gel** is excreted in human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be make whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

During clinical trials, the most frequently reported adverse event in the BenzaClin treatment group was dry skin (12%). The Table below lists local adverse events reported by at least 1% of patients in the BenzaClin and vehicle groups.

Local Adverse Events - all causalities in >/= 1% of patients		
	BenzaClin n = 420	Vehicle n = 168
Application site reaction	13 (3%)	1 (<1%)
Dry skin	50 (12%)	10 (6%)
Pruritus	8 (2%)	1 (<1%)
Peeling	9 (2%)	-
Erythema	6 (1%)	1 (<1%)
Sunburn	5 (1%)	-

The actual incidence of dry skin might have been greater were it not for the use of a moisturizer in these studies.

DOSAGE AND ADMINISTRATION

BenzaClin Topical Gel should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED AND COMPOUNDING INSTRUCTIONS

Size (Net Weight)	**NDC 0066-**	**Benzoyl Peroxide Gel**	**Active Clindamycin Powder (In plastic vial)**	**Purified Water To Be Added**
25 grams	0494-25	19.7g	0.3g	5 mL

Prior to dispensing, tap vial until powder flows freely. Add purified water to vial (to the mark) and immediately shake to completely dissolve clindamycin. If needed, add additional purified water to bring level up to the mark. Add this solution to gel and stir until homogenous in appearance (1 to 1½ minutes). **BenzaClin Topical Gel** should then be stored under refrigeration. Do not freeze. Place a 2-month expiration date on the label immediately following mixing. Place a STORE REFRIGERATED sticker onto the jar.

NOTE:

Prior to reconstitution, store at Controlled Room Temperature 20 to 25°C (68 to 77°F)[see USP].

After reconstitution, store refrigerated 2 to 8°C (36 to 46°F).

Do not freeze. Keep tightly closed. Keep out of the reach of children.
US Patents 5,446,028; 5,767,098; 6,013,637IN-xxxx Rev. mm/yy

DERMIK LABORATORIES, INC.
Berwyn, PA 19312 USA

APPEARS THIS WAY
ON ORIGINAL

/s/

Jonathan Wilkin
12/21/00 12:51:18 PM

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 31

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-756

Dermik Laboratories, Inc.
Attention: Kim Forbes-McKean, Ph.D.
Senior Director, Product Development and Commercialization
1050 Westlakes Drive
Berwyn, PA 19312

Dear Dr. Forbes-McKean:

Please refer to your new drug application (NDA) dated April 9, 1998, received April 10, 1998, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for BenzaClin (clindamycin 1% and benzoyl peroxide 5% gel) Topical Gel.

Please refer to our action letter dated April 1, 1999.

We acknowledge receipt of your submissions dated June 29, July 7, August 4, September 20, and October 17, 2000. Your submission of June 29, 2000, received June 30, 2000, constituted a complete response to our April 1, 1999, action letter.

This new drug application provides for the use of BenzaClin (clindamycin 1% and benzoyl peroxide 5% gel) Topical Gel for the treatment of acne vulgaris.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 50-756." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitments specified in your facsimile dated December 20, 2000. You have agreed to submit the following protocols within 9 months of the approval of this application:

1. To conduct a dermal carcinogenicity study and a study on the effects on UV-induced skin carcinogenicity. These studies should be completed and submitted within 4 years of the approval of this application.

2. To conduct a study in patients with acne vulgaris designed to assess the degree of systemic absorption of clindamycin under maximal use conditions (i.e. maximizing the amount applied, surface area involved, and frequency of application consistent with the approved package insert). Such a study should be done under multiple dosing conditions and include a representative range of ages of both sexes. This *in vivo* pharmacokinetic study should be completed and submitted within 18 months of approval of this application.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your post marketing commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these post marketing commitments must be clearly designated "Post Marketing Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving pediatric studies below the age of 12 years, because acne is not prevalent in the population from birth to 11 years, and this product would not represent a substantive therapeutic benefit as an acne therapy for that population. There are sufficient data to determine efficacy and safety down to and including age 12 years. The Agency grants you a partial waiver for pediatric acne studies for the age group between birth and 11 years of age, under 21 CFR 314.55(c)(4)

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Kevin Darryl White, Project Manager, at (301) 827-2020.

Sincerely,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 50-756
HFD-540/Div. Files
HFD-540/White (with labeling) 11.17.00
HFD-540/Kozma-Fornaro (with labeling) 11.17.00
HFD-540/Wilkin (with labeling)
HFD-540/Walker (with labeling) 11.17.00
HFD-540/Huene (with labeling)
HFD-540/DeCamp (with labeling) 11.21.00
HFD-540Vidra (with labeling) 11.21.00
HFD-540/Jacobs (with labeling) 11.17.00
HFD-540Mainigi (with labeling)
HFD-540/Bashaw (with labeling) 11.21.00
HFD-540/Al-Osh (with labeling)
HFD-540/Thomson (with labeling)
HFD-520/A. Sheldon/Marsik (with labeling)
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-42/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-093/DDMS-IST (with labeling)
HFD-830/DNDC Division Director (with labeling)
DISTRICT OFFICE

Drafted by: KDW 11-17-00 02:45pm
Initialed by:
Final:
Filename: NDA 50-756 BenzaClin AP 11-20-00

APPROVAL (AP)

EXHIBIT 32

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

FINAL PRINTED LABELING

DRAFT
DUAC Topical Gel
(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.
Not for Ophthalmic Use.

Rx Only

DESCRIPTION
DUAC Topical Gel contains clindamycin phosphate, (7(S)-chloro-7-deoxylincomycin-2-phosphate), equivalent to 1% clindamycin, and 5% benzoyl peroxide.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

Clindamycin phosphate is $C_{18}H_{34}ClN_2O_8PS$. The structural formula for clindamycin phosphate is represented below:

[insert structure]

Clindamycin phosphate has a molecular weight of 504.97 and its chemical name is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate).

Benzoyl peroxide is $C_{14}H_{10}O_4$. It has the following structural formula:

[insert structure]

Benzoyl peroxide has a molecular weight of 242.23.

Each gram of DUAC Topical Gel contains 10 mg (1%) clindamycin, as phosphate, and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methylparaben, poloxamer, purified water, and sodium hydroxide.

CLINICAL PHARMACOLOGY
A comparative study of the pharmacokinetics of DUAC Topical Gel and 1% clindamycin solution alone in 78 patients indicated that mean plasma clindamycin levels during the four week dosing period were < 0.5 ng/ml for both treatment groups.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid.

Microbiology:

Mechanism of Action
Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation

of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis. Benzoyl peroxide is a potent oxidizing agent.

***In Vivo* Activity**
No microbiology studies were conducted in the clinical trials with this product.

***In Vitro* Activity**
The clindamycin and benzoyl peroxide components individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this is not known.

Drug Resistance
There are reports of an increase of *P. acnes* resistance to clindamycin in the treatment of acne. In patients with *P. acnes* resistant to clindamycin, the clindamycin component may provide no additional benefit beyond benzoyl peroxide alone.

CLINICAL STUDIES
In five randomized, double-blind clinical studies of 1,319 patients, 397 used DUAC, 396 used benzoyl peroxide, 349 used clindamycin and 177 used vehicle. DUAC applied once daily for 11 weeks was significantly more effective than vehicle, benzoyl peroxide, and clindamycin in the treatment of inflammatory lesions of moderate to moderately severe facial acne vulgaris in three of the five studies (Studies 1, 2, and 5).

Patients were evaluated and acne lesions counted at each clinical visit: weeks 2, 5, 8, 11. The primary efficacy measures were the lesion counts and the investigator's global assessment evaluated at week 11. Patients were instructed to wash the face, wait 10 to 20 minutes, and then apply medication to the entire face, once daily, in the evening before retiring. Percent reductions in inflammatory lesion counts after treatment for 11 weeks in these five studies are shown in the following table:

Mean percent reduction in inflammatory lesion counts					
	Study 1 (n=120)	**Study 2 (n=273)**	**Study 3 (n=280)**	**Study 4 (n=288)**	**Study 5 (n=358)**
DUAC	65%	56%	42%	57%	52%
Benzoyl Peroxide	36%	37%	32%	57%	41%
Clindamycin	34%	30%	38%	49%	33%
Vehicle	19%	-0.4%	29%		29%

The DUAC group showed greater overall improvement in the investigator's global assessment than the benzoyl peroxide, clindamycin and vehicle groups in three of the five studies (Studies 1, 2, and 5).

Clinical studies have not adequately demonstrated the effectiveness of DUAC versus benzoyl peroxide alone in the treatment of non-inflammatory lesions of acne.

INDICATIONS AND USAGE
DUAC Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris

DUAC Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS

DUAC Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

WARNINGS

ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIA IS ONE PRIMARY CAUSE OF ANTIBIOTIC-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERSISTENT DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium difficile* AND STOOL ASSAY FOR *Clostridium difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients: Patients using DUAC Topical Gel should receive the following information and instructions:

1. DUAC Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

2. This medication should not be used for any disorder other than that for which it was

prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.

4. Patients should report any signs of local adverse reactions to their physician.

5. DUAC Topical Gel may bleach hair or colored fabric.

6. DUAC Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.

7. Before applying DUAC Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.

8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with DUAC Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with DUAC Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g DUAC Topical Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with DUAC Topical Gel or benzoyl peroxide. It is also not known whether DUAC Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DUAC Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether DUAC Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS
During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0=absent, 1=mild, 2=moderate, and 3=severe. The percentage of patients that had symptoms present at baseline and during treatment were as follows:

Local reactions with use of DUAC Topical Gel
% of patients using DUAC Topical Gel with symptom present
Combined results from 5 studies (n=397)

	Baseline			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

(Percentages derived by # subjects with symptom score/# enrolled DUAC subjects, n=397).

DOSAGE AND ADMINISTRATION
DUAC Topical Gel should be applied once daily, in the evening or as directed by the physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED
DUAC (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in a 45 gram tube - NDC 0145-2371-05.

Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36 °F and 46°F Do not freeze.

To the Pharmacist: Dispense with a 60 day expiration date and specify "Store at room temperature up to 25°C (77°F). Do not freeze."

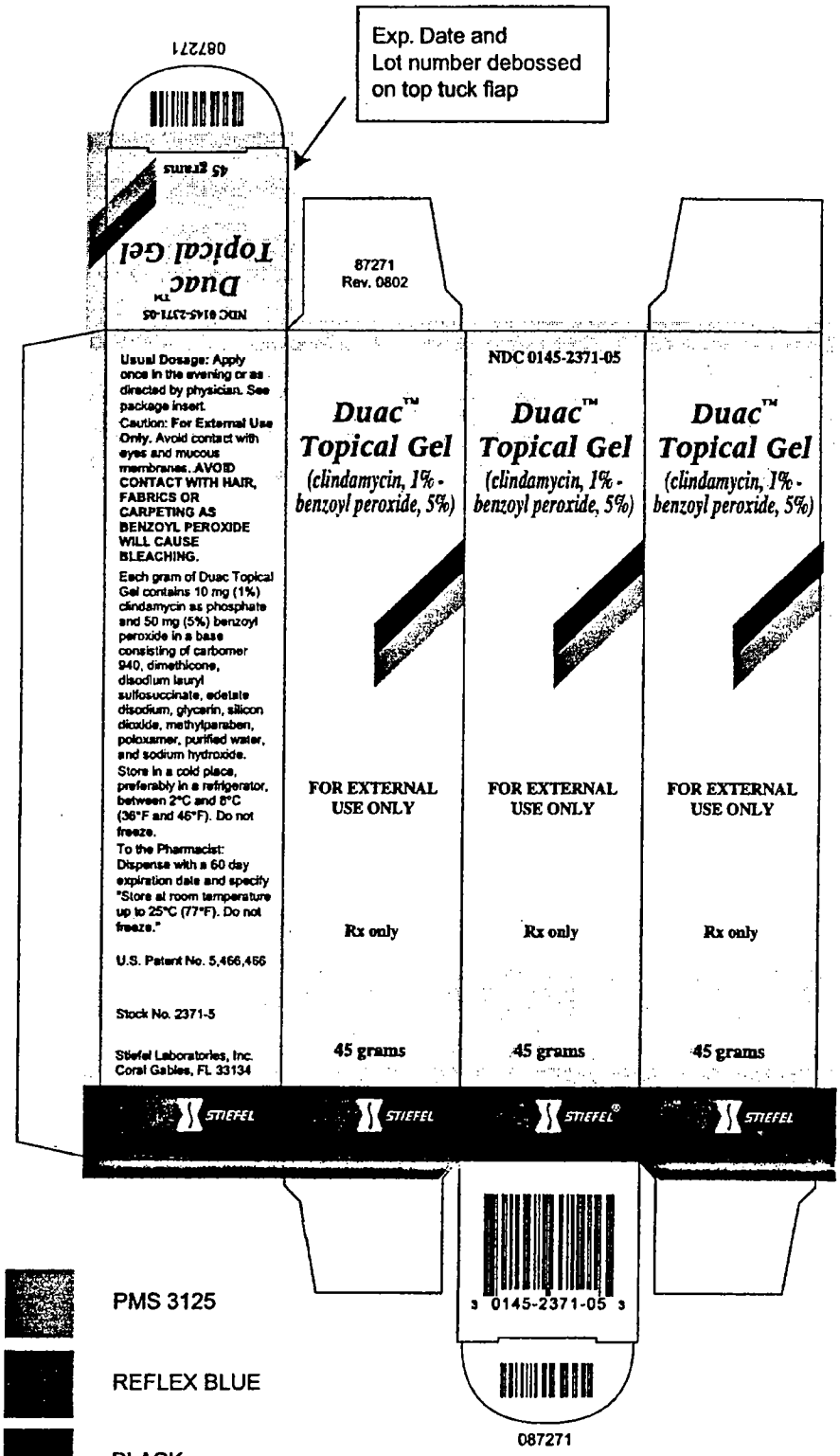
Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent No. 5,466,466

Stiefel logo®
Stiefel Laboratories, Inc.
Coral Gables, FL 33134

86422 Rev. 0802

Actual Size
1-3/8" x 1-3/8" x 6-1/4"



PMS 3125

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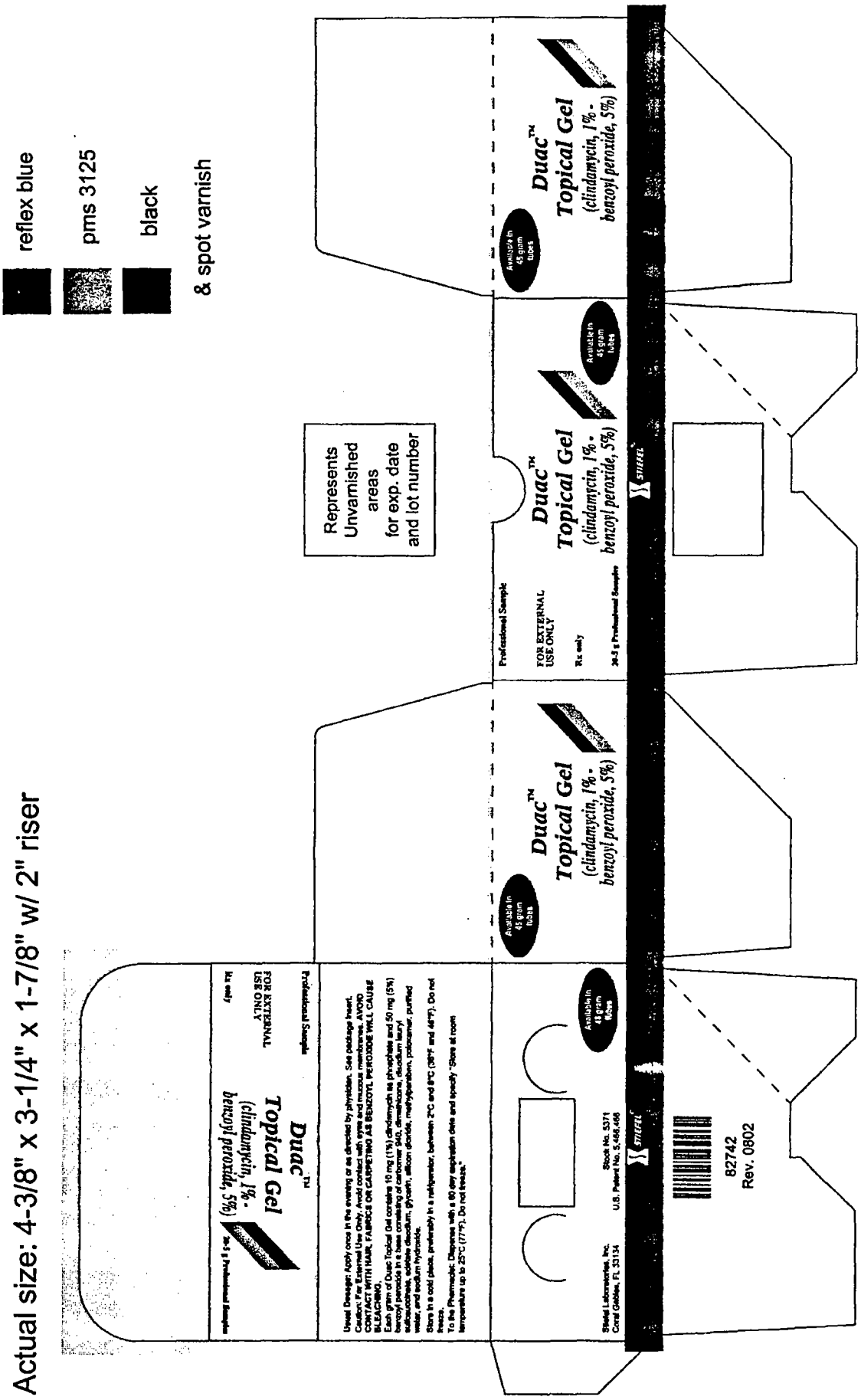
& VARNISH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reflex blue
pms 3125
black
& spot varnish
Represents Unvarnished areas for exp. date and lot number
Duac™ Topical Gel
(clindamycin, 1% - benzoyl peroxide, 5%)
Available in 45 gram tubes
FOR EXTERNAL USE ONLY
Professional Sample
Rx only
Shield Laboratories, Inc.
Coral Gables, FL 33134
U.S. Patent No. 5,468,466
Stock No. 5371
82742
Rev. 0802

Actual size
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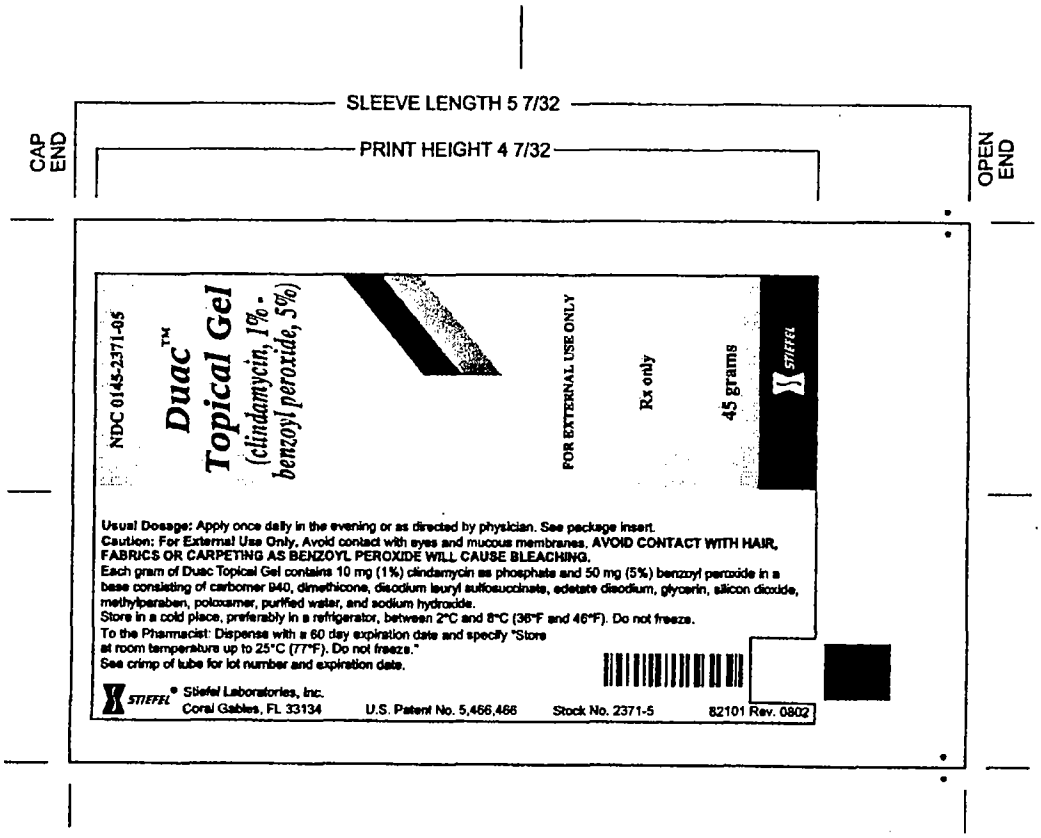

REFLEX BLUE

PMS 3125

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& VARNISH

BAR CODE SHOULD READ 082101

ACTUAL SIZE
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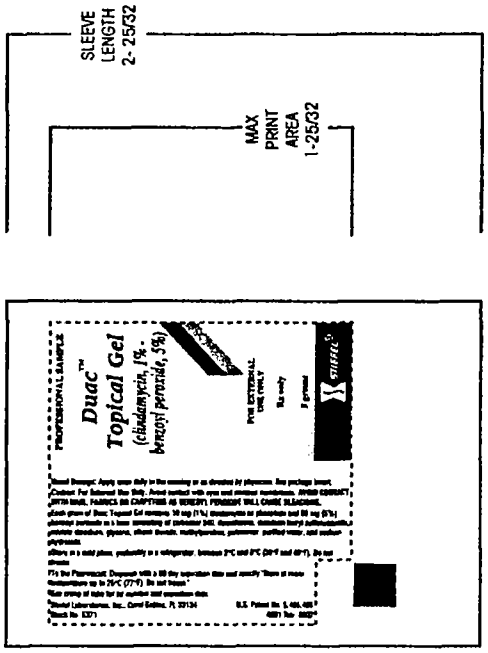
Reflex Blue
PMS 3125
BLACK



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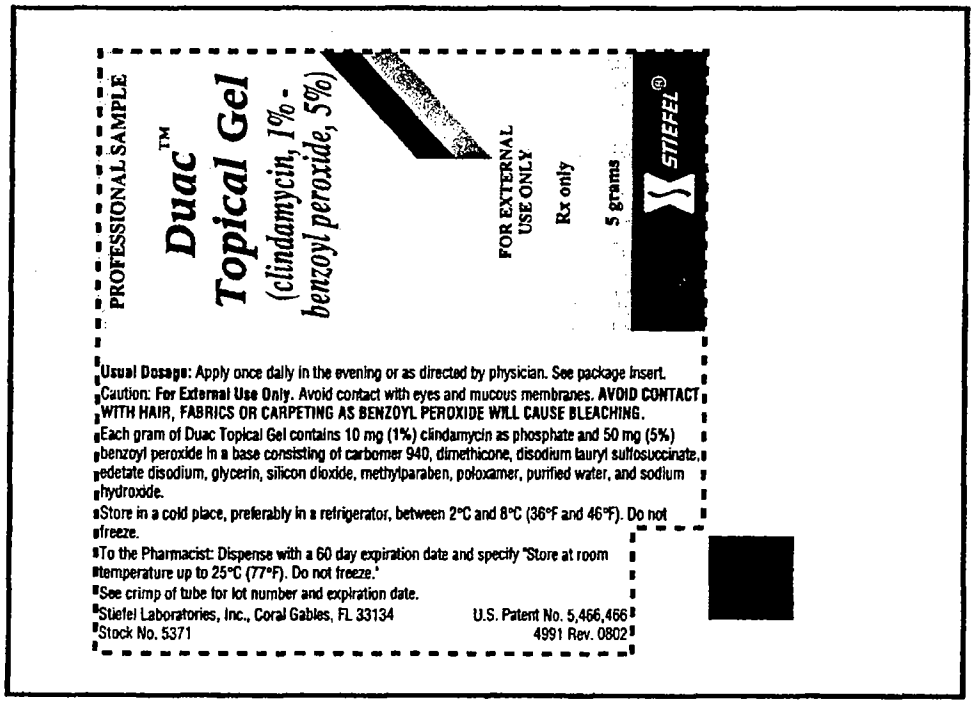


200%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
8/26/02 10:16:30 AM
Per discussion with TL, there was no new information in the safety update that had not been reviewed previously.

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 33

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-741

Stiefel Laboratories, Inc.
Attention: William A. Carr, Jr.
Vice President
Route 145
Oak Hill, New York 12460

Dear Mr. Carr:

Please refer to your new drug application (NDA) dated February 22, 2002, received February 26, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DUAC (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel.

We acknowledge receipt of your submissions dated March 15 (two), June 14, July 9, and August 20, 2002; and facsimile transmission August 5, 2002. Your submission of February 22, 2002, constituted a complete response to our September 6, 2000, action letter.

This new drug application provides for the use of DUAC Topical (clindamycin, 1% - benzoyl peroxide, 5%) Gel for the topical treatment of inflammatory acne vulgaris.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert, immediate container, and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 50-741." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated August 20, 2002. These commitments are listed below.

1. The Applicant commits to performing dermal carcinogenicity testing of the

combination drug product.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 6 months of the date of the approval of the protocol
Final Report Submission:	Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug products on UV-induced skin cancers.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 6 months of the date of the approval of the protocol
Final Report Submission:	Within 12 months after the study completion

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application for pediatric patients below the age of 12.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available

We remind you that you must comply with the requirements for an approved NDA set forth under

21 CFR 314.80 and 314.81.

If you have any questions, call Victoria Lutwak, Project Manager, at 301/827-2073.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 34

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-748

APPROVED LABELING

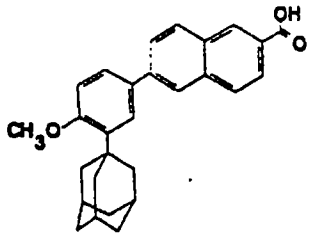
DIFFERIN® **Rx only**

(adapalene)
Cream, 0.1%

For topical use only. Not for ophthalmic, oral, or intravaginal use.

DESCRIPTION: DIFFERIN® (adapalene) Cream, 0.1%, contains adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methylparaben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propylparaben, purified water, squalane, and trolamine.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. It is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.53. Adapalene is represented by the following structural formula.



CLINICAL PHARMACOLOGY:

Mechanism of Action: Adapalene acts on retinoid receptors. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris.

Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Pharmacokinetics: Absorption of adapalene from DIFFERIN® Cream through human skin is low. In a pharmacokinetic study with six acne patients treated once daily for 5 days with 2 grams of DIFFERIN®Cream applied to 1000 cm^2 of acne involved skin, there were no quantifiable amounts (limit of quantification = 0.35 ng/mL) of adapalene in the plasma samples from any patient. Excretion appears to be primarily by the biliary route.

INDICATIONS AND USAGE: DIFFERIN® Cream is indicated for the topical treatment of acne vulgaris.

CLINICAL STUDIES: Two vehicle-controlled clinical studies were conducted in patients 12 to 30 years of age with mild to moderate acne vulgaris, in which DIFFERIN® Cream was compared with its vehicle. Patients were instructed to apply their treatment medication once daily at bedtime for 12 weeks. In one study patients were provided with a soapless cleanser and were encouraged to refrain from using moisturizers. No other topical medications, other than DIFFERIN® Cream, were to be applied to the face during the studies. DIFFERIN® Cream was significantly more effective than its vehicle in the reduction of acne lesion counts. The mean percent reduction in lesion counts from baseline after treatment for 12 weeks are presented in the following table:

MEAN PERCENT REDUCTION IN LESION COUNTS FROM BASELINE TO WEEK 12				
	Study No. 1		Study No. 2	
Efficacy Variable	Adapalene Cream, 0.1% N = 119	Cream Vehicle N = 118	Adapalene Cream, 0.1% N = 175	Cream Vehicle N = 175
Non-inflammatory lesions	34%	18%	35%	15%
Inflammatory lesions	32%	17%	14%	6%
Total lesions	34%	18%	30%	15%

The trend in the Investigator's global assessment of severity supported the efficacy of DIFFERIN® when compared to the cream vehicle.

CONTRAINDICATIONS: DIFFERIN® Cream should not be administered to individuals who are hypersensitive to adapalene or any of the components in the cream vehicle.

PRECAUTIONS:

General: Certain cutaneous signs and symptoms of treatment such as erythema, dryness, scaling, burning, or pruritus may be experienced with use of DIFFERIN® Cream. These are most likely to occur during the first two to four weeks of treatment, are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Depending upon the severity of these side effects, patients should be instructed to reduce the frequency of application or discontinue use.

If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with adapalene.

Information for Patients: Patients using DIFFERIN® Cream should receive the following information and instructions:

1. This medication is to be used only as directed by the physician.
2. It is for external use only.
3. Avoid contact with the eyes, lips, angles of the nose, and mucous membranes.
4. Cleanse area with a mild or soapless cleanser before applying this medication.

5. Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.
6. Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis, and eye irritation.
7. This medication should not be applied to cuts, abrasions, eczematous or sunburned skin.
8. Wax epilation should not be performed on treated skin due to the potential for skin erosions.
9. During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of this medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Overall clinical benefit may be noticed after two weeks of therapy, but at least eight weeks are required to obtain consistent beneficial effects.

Drug Interactions: As DIFFERIN® Cream has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime rind) should be approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN® Cream. If these preparations have been used, it is advisable not to start therapy with DIFFERIN® Cream until the effects of such preparations in the skin have subsided.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*:** Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day, and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day. These doses are up to 8 times (mice) and 6 times (rats) in terms of mg/m^2/day the maximum potential exposure at the recommended topical human dose (MRHD), assumed to be 2.5 grams DIFFERIN® Cream, which is approximately 1.5 mg/m^2 adapalene. In the oral study, increased incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats was observed.

No photocarcinogenicity studies were conducted. Animal studies have shown an increased risk of skin neoplasms with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human

use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vivo* (mouse micronucleous test) and *in vitro* (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) studies.

Reproductive function and fertility studies were conducted in rats administered oral doses of adapalene in amounts up to 20 mg/kg/day (up to 80 times the MRHD based on mg/m^2 comparisons). No effects of adapalene were found on the reproductive performance or fertility of the F_0 males or females. There were also no detectable effects on the growth, development and subsequent reproductive function of the F_1 generation.

Pregnancy: **Teratogenic effects. Pregnancy Category C.** No teratogenic effects were seen in rats at oral doses of 0.15 to 5.0 mg/kg/day adapalene (up to 20 times the MRHD based on mg/m^2 comparisons). However, adapalene administered orally at doses of ≥ 25 mg/kg, (100 times the MRHD for rats or 200 times MRHD for rabbits) has been shown to be teratogenic. Cutaneous teratology studies in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day (24 times the MRHD for rats or 48 times the MRHD for rabbits) exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN® Cream is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric use: Clinical studies of DIFFERIN® Cream were conducted in patients 12 to 30 years of age with acne vulgaris and therefore did not include subjects 65 years and older to determine

whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS:

In controlled clinical trials, local cutaneous irritation was monitored in 285 acne patients who used DIFFERIN® Cream once daily for 12 weeks. The frequency and severity of erythema, scaling, dryness, pruritus and burning were assessed during these studies. The incidence of local cutaneous irritation with DIFFERIN® Cream from the controlled clinical studies is provided in the following table:

Incidence of Local Cutaneous Irritation with DIFFERIN® Cream from Controlled Clinical Studies (N-285)

	None	Mild	Moderate	Severe
Erythema	52% (148)	38% (108)	10% (28)	<1% (1)
Scaling	58% (166)	35% (100)	6% (18)	<1% (1)
Dryness	48% (136)	42% (121)	9% (26)	<1% (2)
Pruritus (persistent)	74% (211)	21% (61)	4% (12)	<1% (1)
Burning/Stinging (persistent)	71% (202)	24% (69)	4% (12)	<1% (2)

Other reported local cutaneous adverse events in patients who used DIFFERIN® Cream once daily included: sunburn (2%), skin discomfort-burning and stinging (1%) and skin irritation (1%). Events occurring in less than 1% of patients treated with DIFFERIN® Cream included: acne flare, dermatitis and contact dermatitis, eyelid edema, conjunctivitis, erythema, pruritus, skin discoloration, rash, and eczema.

OVERDOSAGE: DIFFERIN® Cream is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, scaling, or skin discomfort may occur. The acute oral toxicity of DIFFERIN® Cream in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: DIFFERIN Cream should be applied to affected areas of the skin, once daily at nighttime. A thin film of the cream should be applied to the skin areas where acne lesions appear, using enough to cover the entire affected area lightly. A mild transitory

sensation of warmth or slight stinging may occur shortly after the application of DIFFERIN® Cream.

HOW SUPPLIED: DIFFERIN® (adapalene) Cream, 0.1% is supplied in the following sizes.

15g tube - NDC 0299-5915-15

45g tube - NDC 0299-5915-45

Storage: Store at controlled room temperature 68° to 77° F (20° - 25°C) Protect from freezing.

Marketed by:
Galderma Laboratories, L.P.
Fort Worth, Texas 76133 USA

Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA

GALDERMA is a registered trademark.

Revised: May 25, 2000.

45 GRAM CARTON

Principal Display Panel

NDC 0299-5915-45 **Rx Only**

DIFFERIN® (adapalene) Cream, 0.1%

GALDERMA (Logo)

NET WT. 45 g

Back Information Panel

For topical use only. Not for ophthalmic, oral, or intravaginal use.

Store at controlled room temperature 68° to 77°F (20° - 25°C). Protect from freezing.

Usual dosage: Apply a thin film once a day at nighttime to affected areas. See package insert for complete prescribing information.

Contains: adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methylparaben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propylparaben, purified water, squalane, and trolamine.

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76133 USA
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA
GALDERMA is a registered trademark.
(part number) 0300

Bottom Tuck Flap

Lot:

Expires:

45 GRAM PRIMARY CONTAINER (TUBE) LABEL

Principal Display Panel

NDC 0299-5915-45 **Rx Only**

DIFFERIN® (adapalene) Cream, 0.1%

GALDERMA (Logo)

NET WT. 45 g

Information Panel

For topical use only. Not for ophthalmic, oral, or intravaginal use.

Store at controlled room temperature 68° to 77°F (20° - 25°C). Protect from freezing.

Usual dosage: Apply a thin film once a day at nighttime to affected areas. See package insert for complete prescribing information.

Contains: adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methylparaben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propylparaben, purified water, squalane, and trolamine.

Lot no. and expiration date on crimp.

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76133 USA
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA
GALDERMA is a registered trademark.
(part number) 0300

15 GRAM CARTON

Principal Display Panel

NDC 0299-5915-15 **Rx Only**

DIFFERIN® (adapalene) Cream, 0.1%

GALDERMA (Logo)

NET WT. 15 g

Information Panel

For topical use only. Not for ophthalmic, oral, or intravaginal use.

Store at controlled room temperature 68° to 77°F (20° - 25°C). Protect from freezing.

Usual dosage: Apply a thin film once a day at nighttime to affected areas. See package insert for complete prescribing information.

Contains: adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methylparaben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propylparaben, purified water, squalane, and trolamine.

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76133 USA
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA
GALDERMA is a registered trademark.
(part number) 0300

Bottom Tuck Flap
Lot:
Expires:

15 GRAM PRIMARY CONTAINER (TUBE) LABEL

Principal Display Panel

NDC 0299-5915-15 **Rx Only**

DIFFERIN® (adapalene) Cream, 0.1%

GALDERMA (Logo)

NET WT. 15 g

Information Panel

For topical use only. Not for ophthalmic, oral, or intravaginal use.

Store at controlled room temperature 68° to 77°F (20° - 25°C). Protect from freezing.

Usual dosage: Apply a thin film once a day at nighttime to affected areas. See package insert for complete prescribing information.

Contains: adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methylparaben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propylparaben, purified water, squalane, and trolamine.

Lot no. and expiration date on crimp.

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76133 USA
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA
GALDERMA is a registered trademark.
(part number) 0300

2 GRAM PHYSICIAN SAMPLE (TUBE) LABEL

Principal Display Panel

NDC 0299-5915-02 Rx Only

DIFFERIN® (adapalene) Cream, 0.1%

NET WT. 2 g SAMPLE, NOT FOR SALE

Information Panel

For topical use only. Not for eye use.

Store at 68° - 77°F (20° - 25°C). Do not freeze.

Usual dosage: See package insert.

Lot no. and exp. date on crimp.

Mktd. by:

GALDERMA LABORATORIES, L.P.

Ft. Worth, TX 76133 USA

(part number) 0300

EXHIBIT 35

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-748

APPROVAL LETTER

MAY 26 2000

NDA 20-748

Galderma Laboratories, L.P.
Attention: Ms. Christine Shank
Director, Regulatory Submissions
P.O. Box 331329
Fort Worth, TX 76163-1329

Dear Ms. Shank:

Please refer to your new drug application (NDA) dated July 16, 1997, received July 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DIFFERIN® (adapalene) Cream, 0.1%.

We acknowledge receipt of your submissions dated April 24 and 28, May 8, 24(2 facsimiles), 25(facsimile) and 26(facsimile), 2000. Your submissions dated March 9, and March 31, 2000, together constituted a complete response to our March 8, 2000, action letter.

This new drug application provides for the use of DIFFERIN® (adapalene) Cream for the topical treatment of acne vulgaris.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-748." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application for pediatric patients below the age of 12 years. The necessary studies are impossible or highly impractical to conduct because the number of patients is too small.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Olga Cintron, Project Manager, at (301) 827-2020.

Sincerely,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-748
HFD-540/Div. Files
HFD-540/O.Cintron
HFD-540/CPMS/Kozma-Fornaro (with labeling).
HFD-540/Division Director/Wilkin (with labeling)
HFD-540/Clinical TL/Walker (with labeling)
HFD-540/Clinical Reviewer/Huene (with labeling)
HFD-540/Chemistry TL/DeCamp (with labeling)
HFD-540/Chemist/Timmer (with labeling)
HFD-540/Pharm/Tox Reviewer/Mainigi (with labeling)
HFD-540/Pharm/Tox TL/ Jacobs (with labeling)
HFD-160/Microbiologist/Greenman (with labeling)
HFD-160/Microbiology TL/Cooney (with labeling)
HFD-880/Biopharmaceutics Reviewer/Lee (with labeling)
HFD-880/Biopharmaceutics TL/Bashaw (with labeling)
HFD-725/Biostatistician/Farr (with labeling)
HFD-725/Biostatistics TL/Al-Osh (with labeling)
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-46/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-830/DNDC Division Director
DISTRICT OFFICE

Drafted by: OC/May 9, 2000
Initialed by:
final:
filename: ADAPALEN.APL

APPROVAL (AP)